TOBACCO INDUSTRY RESEARCH COMMITTEE
150 EAST FORTY SECOND STREET
NEW YORK 17, N.Y.

#234
Cf. #155
(Activated 7/1/57
Renewed 7/1/58)

Application For Research Grant

Date: April 13, 1959

1. Name of Investigator: Duane G. Wenzel, Ph.D.

2. Title: Professor of Pharmacology

3. Institution
& Address: The School of Pharmacy
University of Kansas
Lawrence, Kansas

4. Project or Subject: A Study of the Role of Sympathomimetic Amines in the Interaction of Nicotine and Cholesterol upon the Myocardium.

5. Detailed Plan of Procedure (Use reverse side if additional space is needed):

Prior Work on This Project. Studies completed by the applicant demonstrate that nicotine administered to rabbits fed a low (0.1%) cholesterol diet produces significant increases in plasma cholesterol (1); that chickens give equivocal results (2); and that rabbits fed a 1% cholesterol-5% oil diet respond to nicotine with an increase in cardiac pathology (3). Present studies include an examination of peripheral vascular effects in rabbits and the response of the rat to nicotine and hypercholesterolemia.

Background to Proposal. Epinephrine and norepinephrine have been demonstrated to produce tissue hypoxia and necrosis (4). In large doses, injury to the media has been produced (5) while repeated smaller doses produces damage to the intima (6) and cause an increase of cholesterol in this tissue (7). Similar effects have been reported from the stimulation of the sympathic ganglia (8). Recent evidence indicates that epinephrine and norepinephrine are avidly stored in the myocardium (9) and that they can be released by an electrical stimulus (10). Further, it has been demonstrated that the stimulant effect of nicotine upon the atria is dependent upon the release of epinephrine (11). Russian studies (12) have found that amphetamine produces an increase in both blood lipids and atherosclerosis. Finally, as presented by Rosenman (13) there are good clinical indications that stress, at least in part through the release of epinephrine, produces: (1) organic vascular damage predisposing to lipid deposition; (2) an increase in plasma cholesterol; and (3) a decrease in blood coagulation time.

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Proposal. On the basis of the foregoing and similar additional evidence, it is suggested that the observed interaction between nicotine and hypercholesterolemia upon the myocardium is related to the release of catecholamines. It is proposed that this hypothesis be tested directly in the following manner: Separate groups of rabbits would be established with the following regimens: (1) Control, (2) Nicotine, (3) Cholesterol 1% and oil 5%, (4) Nicotine and cholesterol, (5) A sympathomimetic amine such as ephedrine and cholesterol, (6) Nicotine and cholesterol and 1-(3',4'-dichlorophenyl)-2-isopropylaminoethanol HCl (DCI Lilly), (7) Nicotine and cholesterol and reserpine, and (8) Nicotine and cholesterol and iproniazid.

The rationale for the use of the proposed dietary additives is as follows: The use of a stable sympathomimetic amine such as ephedrine in the drinking water would provide a sympathomimetic effect similar to that of epinephrine or norepinephrine, yet could yield information as to their specificity. The administration of DCI, a potent blocking agent to the effect of the epinephrine on the heart, would indirectly determine the effect of the endogenous catecholamines. Reserpine, having been demonstrated to deplete the myocardium of catecholamines may then also provide protection to any effects of nicotine mediated through the catecholamines. Iproniazid, an agent with beneficial action in angina pectoris, produces a long lasting rise in the catecholamine content of the heart, yet its pharmacological effects on this organ cannot be explained on the basis of a catecholamine effect. It has been suggested that it may inhibit the release of these substances or prevent the formation of harmful metabolic products (14).

The study would continue for 24 weeks, during which time blood coagulation times and plasma cholesterol levels would be determined. At the termination of the study, cardiovascular micropathology would be performed.

REFERENCES

(1) Wenzel, D. G. and Beckloff, G.L., J. Am. Pharm. Assoc., 47, 338 (1958).
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(5) Hueper, W. C., Arch. Path., 39,51(1945)
(6) Waters, L. L., The Reaction of the Artery Wall to Hypertension and to Hypervolemia Symposium on Atherosclerosis, National Academy of Science, National Research Council, Publication No. 338, 1955.
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(12) Myasnikov, A. L., Circulation, 17, 99 (1958).
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6. Budget Plan:

Salaries	$5,400.
Expendable Supplies	600.
Permanent Equipment	900.
Overhead (15%)	1,065.
Other (travel)	200.
Total	$8,165.

7. Anticipated Duration of Work:

September 1, 1959 through August 31, 1960

8. Facilities and Staff Available:

An air-conditioned animal room and several completely equipped research laboratories are available. The project director will be available on a full-time basis for two summer months and part-time throughout the year. Other personnel will include Dr. James A. Turner, assistant Professor of Pathology, a one-half time research assistant, a pathology technician, and an animal room caretaker.

9. Additional Requirements:

None.

10. Additional Information (including relation of work to other projects and other sources of supply):

None.

/s./ Duane G. Wenzel
Director of Project

/s./ William J. Argersinger, Jr.
Assoc. Dean Graduate School

Business Officer of the Institution

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